

A method for the production of a biologically active prosthetic device for the reconstruction of bone tissue and the prosthetic device itself

The present invention relates to a method for the production of a biologically active prosthetic device for the reconstruction of bone tissue and the prosthetic device itself.

5 More specifically, the method according to the present invention involves obtaining a made to measure prosthetic device identical to a bone defect or lacuna to be filled in a patient, and which is made of a biologically active material, that is to say, a Ca/P-based ceramic synthesis material (calcium phosphate material, i.e.: stoichiometric hydroxyapatite; non-stoichiometric hydroxyapatite: carbonated hydroxyapatite (mainly of type B); hydroxyapatite enriched with magnesium or fluoride or with strontium or sodium; carbonated hydroxyapatite enriched with magnesium; hydroxyapatite/ β tricalcium phosphate in proportions of 50% - 50%, 70% - 30%, 30% - 70%; alpha-tricalcium phosphate (α TCP); beta-tricalcium phosphate (β TCP); mixtures of alpha-tricalcium

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phosphate (α TCP) and beta-tricalcium phosphate (β TCP) with predetermined and interconnected porosity in the 30 - 90% range with bimodal distribution of the dimensions of the pores in the
5 0.1 - 125 microns and 125 - 2500 microns range.

The prosthetic device according to the present invention is obtained with a new production technology and is used for a new bone reconstruction technique.

10 Having achieved the primary objective of saving the patient's life, in its latest scientific and technological evolution, surgery aims in its most advanced area of development to improve the patient's quality of life, making the surgical
15 solutions adopted more acceptable for the patient in functional and aesthetic terms.

It is currently possible to carry out operations substituting both hard tissue and very extensive tissue.

20 In parallel, biotechnologies, with great progress made in molecular biology, have undergone enormous growth particularly in the last decade.

Genetic engineering and prosthetic engineering were a driving force behind research and development of
25 new systems for the production of medical devices,

in terms of both materials and components, to allow clinical solutions whose size and quality are suitable for the individual, specific patient and are the main driving forces in the field of biomedical research for this type of clinical applications..

At present in the reconstruction of lacunae in bones, such as parts of the cranium, maxillofacial zones or parts of long bones (for example the femur), parts of bone are used which are taken from the patient (autologous transplant) or from other persons (heterologous transplant) or artificial materials such as: metals (gold, steel, titanium, tantalum) in the form of plates or meshes or in elongated form, polymers (Nylon, Polyethylene), cements (PMMA: polymethyl methacrylate) and porous bio-ceramic materials, for example ceratite and hydroxyapatite.

Each of these materials has pros and cons, but as a whole porous bio-ceramic materials have some important advantages: the possibility of practically unlimited supplies, unlike transplants using biological materials (autologous or heterologous bone) in which the bone to be used must be taken from the patient or a donor, the fact

that they are biologically active materials and so promote bone regeneration, and the quality of being recognised as inorganic material not alien to the patient and so free of the problems of rejection.

5 There are basically two types of surgical reconstruction techniques: manual modelling during an operation of the prosthetic device which must be implanted and must fill the lacuna in the bone, or it is possible to implant a prosthetic device
10 already produced and modelled to size for the specific lacuna in the patient's bone before the operation.

 The fact that a prosthetic device to be substituted is already ready with the shape and
15 dimensions made to measure for the patient's lacuna makes the surgery much faster and simpler, however, the production of a prosthetic device with shape and dimensions already suitable for the patient's specific lacuna
20 involves difficulties, and the current technique for the production of these devices does not yet give satisfactory results when the above-mentioned bio-ceramic materials are used.

 More precisely, due to the intrinsic
25 characteristics and porosity of the above-

mentioned bio-ceramic materials, when a substitute part for a lacuna in a bone is slip cast using bio-ceramic material, it is difficult to obtain a part with the allocated shape and dimensions.

In particular, it is difficult to obtain a part which precisely substitutes a lacuna in a bone to be filled because the above-mentioned bio-ceramic materials are subject to variations in shape and size retraction during both drying after slip casting and after firing.

One aim of the present invention is to present an improved method for the production of a prosthetic device for the reconstruction of bone tissue with size and shape characteristics identical to the section of bone missing from the patient without the need for adaptations during insertion of the prosthetic device.

Another aim of the present invention is to present an improved method for the production of a prosthetic device for the reconstruction of bone tissue which is made of biologically active material with a controlled-porosity ceramic component.

In accordance with one aspect of the present

invention, a method is proposed for the production of a prosthetic device for the reconstruction of bone tissue as specified in claim 1.

5 Yet another aim of the present invention is the production of a prosthetic device made of biologically active material with a ceramic component having controlled and interconnected porosity in the 30 - 90% range, with bimodal
10 distribution of the dimensions of the pores in the 0.1 - 125 microns and 125 - 2500 microns range, and with bioactivity characteristics, through the osteoconductive properties of the Ca/P-based material, able to contribute to bone
15 regeneration mechanisms, so as to promote the laying down and regrowth of bone tissue.

In accordance with another aspect of the present invention, a prosthetic device is proposed which is made of biologically active material with a
20 porous structure as specified in claim 8.

The dependent claims refer to preferred and advantageous embodiments of the invention.

Embodiments of the present invention, shown by way of example only and without limiting the
25 scope of the invention, are described below with

reference to the accompanying drawings, in which:

- 5 - Figure 1 illustrates a computer model of a patient's cranium in which there is a lacuna in the bone;
- Figures 2 and 3 illustrate a resin model obtained from the computer model shown in the previous figure;
- 10 - Figures 4 and 5 illustrate two successive steps of the method in accordance with the present invention;
- Figure 6 is a cross-section of the cranium illustrated in the previous figures during the step relative to Figure 5;
- 15 - Figure 7 illustrates another application of the present invention relative to long bones, for example a femur, in particular illustrating a patient's femur with a missing central part;
- Figure 8 illustrates the femur shown in the previous figure with a prosthetic device in
20 accordance with the present invention;
- Figure 9 is a front view of a computer model of the femur illustrated in the previous figures with the central part missing (a lacuna in the
25 bone) and a control mould for a prosthetic

device; and

- Figure 10 is a cross-section of the mould illustrated in the previous figure.

The method for the production of a prosthetic device for the reconstruction of bone tissue in accordance with the invention basically comprises the following steps:

1. CAT (Computerised Axial Tomography) scan of the patient and creation of a CAT file representing the three-dimensional electronic model 1 (Figures 1 and 7) of the part of the bone and the bone defect 2 to be reconstructed;

2. based on the data obtained from the CAT (Computerised Axial Tomography) scan of the patient and the CAT file, rapid main and interface software system controlled prototyping is used to create a prototype resin model 3 (Figures 2, 3 and 9) of the area of the patient's bone involved, for example the model 3 may be obtained using the three-dimensional stereolithographic technique;

3. this resin prototype is used to make, with slip casting forming technology, the model 4 (in calcium sulphate, resins or silicone rubbers) of the patient's bone defect to be reconstructed;

4. the model in the previous point is used to

make a mould 5 (Figures 5, 6, 9 and 10) out of calcium sulphate, resins or silicone rubbers which is a negative of the patient's bone defect, again using slip casting forming technology. To obtain this mould a kind of barrier 6 (Figures 5 and 6) or a containment mould 7 (Figure 9) is made using suitable material (for example clay, plasticine or modelling paste) around the bone defect 2 area. The mould 5 made of calcium sulphate, resins or silicone rubbers is then slip cast in this barrier 6 (or containment mould 7) and will serve as a control for the shape and dimensions of the prosthetic device. For said control, the mould 5 has means 8 (Figures 6 and 9) able to detect any points of contact between the semi-finished product and the mould 5. These means 8 may be, for example a coating of tracing paper which can be coloured at points of contact;

5. production of a semi-finished product (not illustrated) already sintered, with controlled and interconnected porosity (30 - 90%) having pore dimensions in the 0.1 - 125 microns and 125 - 2500 microns range made of Ca/P-based biologically active ceramic materials. These materials may be the material described in Italian patent IT-1 307

292 or the material described in the application for a European patent EP-1 411 035 (and in the corresponding application for an Italian patent BO2002A000650). During this step the semi-finished product is made with dimensions larger than and shapes close to those of the model of the patient's bone defect;

6. mechanical processing and manual finishing of the sintered semi-finished product with controlled and interconnected porosity (30 - 90%) with bimodal distribution of the dimensions of the pores in the 0.1 - 125 microns and 125 - 2500 microns range, made of Ca/P-based ceramic material using as a shape and size comparator the negative mould of the patient's bone defect (point 4), to obtain a finished ceramic component corresponding to the patient's bone defect to be filled; mechanical processing and finishing are carried out by removing excess material with diamond milling cutters;

7. the final check of the finished ceramic component, that is to say, the prosthetic device 9 (Figure 8), in terms of dimensions and shape, is carried out directly on the resin model of the area of the patient's bone involved - made in point 2 -

and using the negative mould 6 or 7 obtained in point 4.

It should be noticed that the mechanical processing for removal of material which allows obtainment of the dimensions and shape of the prosthetic device which must fill the bone defect is necessary because Ca/P-based porous ceramic material cannot be slip cast directly with the shape and dimensions required because it is subject to retraction and variations in shape which cannot be foreseen.

Therefore, a part must be made of porous ceramic material which is close to but slightly larger than the required shape and dimensions of the bone defect to be reconstructed.

The shape and precise dimensions of the prosthetic device 9 will then be achieved by means of successive approximations by manually removing material with diamond milling cutters which turn at high speed. Removal of material must be manual because porous ceramic material does not withstand mechanical processing by machine tools, for example, those of the numeric control type, since it would break.

Manual processing to remove material is essential because only an expert operator has the sensitivity

required to avoid breaking the ceramic material. The check to ensure that the shape and precise dimensions of the prosthetic device 9 have been achieved takes place as indicated above with successive checks on the resin model 3 and with the aid of the control mould 5 and the means 8 able to detect any points of contact between the semi-finished product and the mould 5.

The prosthetic device disclosed is characterised in particular by the following aspects:

the shape and dimensions derive from a model of the area of the patient's bone involved, the model being obtained using rapid prototyping technology; its structure has a predetermined and interconnected porosity (30 - 90%) with bimodal distribution of the dimensions of the pores in the 0.1 - 125 microns and 125 - 2500 microns range, and is made of Ca/P-based ceramic synthesis material (Hydroxyapatite, Tricalcium Phosphate or mixtures of them) using technologies for the impregnation/imbibition of porous supports (cellulose, polyurethane, resin), gel-casting, low pressure injection moulding.

The production process flow refers to the following steps:

- CAT scan of the patient and creation of the CAT file (Figure 1);
- reading of the CAT file and check of the extent of the bone defect;
- 5 - production of the model of the area of the patient's bone involved using resin with rapid prototyping (Figures 2 and 3);
- production of the model of the bone defect using calcium sulphate, resins or silicone rubbers
- 10 (Figure 4);
- production of a negative mould of the bone defect using calcium sulphate, resins or silicone rubbers (Figures 5 and 6);
- production of a sintered semi-finished product
- 15 with dimensions greater than and shape similar to the bone defect, having controlled and interconnected porosity (30 - 90%) with pore dimensions in the 0.1 - 125 microns and 125 - 2500 microns range, using Ca/P-based ceramic material;
- 20 - mechanical processing for removal of material and finishing of the porous ceramic component;
- check of the size and shape of the porous ceramic component on the resin model of the area of the bone involved and with the negative of the bone
- 25 defect;

- washing, drying and packaging of the porous ceramic component;
- sterilisation with gamma rays.

The materials which can be used to make the prosthetic device disclosed are:

stoichiometric hydroxyapatite; non-stoichiometric hydroxyapatite: carbonated hydroxyapatite (mainly of type B); hydroxyapatite enriched with magnesium or fluoride or with strontium or sodium; carbonated hydroxyapatite enriched with magnesium; hydroxyapatite/ β tricalcium phosphate in proportions of 50% - 50%, 70% - 30%, 30% - 70%; alpha-tricalcium phosphate (α TCP); beta-tricalcium phosphate (β TCP); mixtures of alpha-tricalcium phosphate (α TCP) and beta-tricalcium phosphate (β TCP), finally more specifically the materials mentioned above and forming the subject matter of patents IT-1 307 292 and EP-1 411 035 (and the corresponding application for an Italian patent BO2002A000650).

The following is a description of several examples of applications of the invention, provided by way of example only and without limiting the scope of the invention.

In a first example, the made to measure prosthetic

device has the following application:
reconstruction of extensive sections of the cranial
theca (neurosurgery).

Accidents involving head trauma have become
particularly frequent in recent years proportional
with the increase in road traffic, accidents at the
workplace or during leisure time. Serious head
traumas often involve brain function, which takes
priority over other lesions, whose future
preservation becomes the neurosurgeon's priority.

A second cause may be skin tumours or rejection
phenomena following the use of other materials, for
which the treatment requires surgical removal as a
last resort.

In all of these cases the surgical treatment is
based on the removal of extensive sections of bone
tissue with consequent primary problems of brain
safety and, second in order of priority, aesthetic
implications.

To solve and overcome these clinical problems, for
reconstruction of the cranial theca a prosthetic
device was produced, which forms the subject matter
of the present invention, "made to measure" and
identical to the lacuna in the bone to be filled,
using hydroxyapatite with controlled and

interconnected porosity (45 - 65%) with objective clinical evidence showing immediate advantages, from an aesthetic viewpoint, but above all in terms of biocompatibility, which other materials cannot fully guarantee.

The surgical technique, not innovative in itself, involves detachment of tissues from the edge of the defect and insertion of the made to measure prosthesis by slotting into place; fixing it with simple wiring thanks to the holes in the "made to measure" prosthesis.

In a second example, the made to measure prosthetic device has the following application: lifting the buccal cavity (dental surgery).

Loss of the upper back teeth often leads to vertical bony atrophy of the alveolar ridge to a certain extent, such that titanium implants cannot be inserted. Today, it is already possible to successfully lift the buccal cavity by means of bone graft according to the Caldwell - Luc technique, but insertion of implants in a single step cannot also be guaranteed.

Therefore, in these cases the buccal cavity lift is normally done first, using autologous or homologous bone, then insertion of the implants after 6

months.

However, observing biological principles, it is possible to use "made to measure prostheses" made of hydroxyapatite with controlled and interconnected porosity (40 - 60%) which allow immediate insertion of the titanium implant, at the same time allowing clotting and its transformation into bone.

The clinical example involved the use of a prosthetic device disclosed, "made to measure" using hydroxyapatite with controlled and interconnected porosity (40 - 60%) which made it possible to insert the titanium implants in a single step, thus achieving a primary stability that would otherwise be difficult.

The surgical technique, also not innovative in itself, involves opening of the buccal cavity from the side and insertion of the made to measure prosthesis in the space obtained.

In a third example, the made to measure prosthetic device has the following application:

ceramic support (scaffold) on which staminal cells can be "sown" for repairing long bones (orthopaedic surgery, maxillofacial surgery).

Progress in knowledge of cellular biology and

improvements in culture techniques make it possible to imagine and in some cases achieve in vitro reconstruction of skeletal tissues able to substitute sick ones.

5 In the specific case for this application a pre-shaped device was produced using hydroxyapatite with controlled and interconnected porosity (55 - 85 %) modelled, with the same design and production criteria as the previous examples, in the
10 dimensions and shape of the sick bone to be substituted and able to be attached to the staminal cells previously taken from the patient's bone marrow then expanded in vitro.

With this system, hydroxyapatite with controlled
15 and interconnected porosity is used as a "scaffold" in which the staminal cells (expanded in vitro) are placed. Once they make contact with the ceramic support, the staminal cells start proliferating, becoming different and generating new bone tissue.

20 The next step, as in the other cases, consists of surgically replacing the sick or damaged bone with this synthetic - organic bone. Again, the operating technique, not innovative in itself, involves substitution of the damaged section with a made to
25 measure prosthesis (to which the autologous

staminal cells were previously added) secured by a Kirsh thread or by wiring.

The positive results of these transplants are guaranteed by the use of a synthetic material (Ca/P compounds such as: stoichiometric hydroxyapatite, non-stoichiometric hydroxyapatite, carbonated hydroxyapatite, doped hydroxyapatites, tricalcium phosphate or mixtures of them) chemically similar to the inorganic component of the bone tissue and of cells which the immune system recognises as its own. With the passage of time (several months) the "device" surgically inserted is slowly transformed into bone, binding perfectly with the surrounding tissue.

This material constitutes, by the interconnections of the channels, the ideal foundation for allowing the growth of bone tissue inside it, since it acts as a vascular support for the newly formed tissue, also promoting bone mineralisation for the specific dimensions of the pores.

The part of the bone missing is substituted by an identical segment of bone perfectly similar to the part removed, but made synthetically in a laboratory and no longer removed from other individuals.

Moreover, another advantage of the bone device disclosed is that it may form a support (scaffold) for the connection to it of cells and/or growth factors in order to create an osteoinductive effect and/or a support for "drug release" with which drugs and/or chemotherapeutic substances can be associated in medical or oncological therapies.

In the case of flat bones (like those of the cranium) the preferred material is a ceramic of the type described in Italian patent IT-1 307 292, that is to say, a ceramic material with less porosity and greater mechanical strength.

In the case of long bones (for example the femur) the preferred material is a ceramic of the type described in the application for a European patent EP-1 411 035 (and in the corresponding application for an Italian patent BO2002A000650), that is to say, a ceramic material with greater porosity which acts as a scaffold for bone restructuring.

The invention described is subject to modifications and variations without thereby departing from the scope of the inventive concept as described in the claims.